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Plasma prostaglandin $F_{2\alpha}$ and plasma 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ levels in women during induction of labor with i.v. infusion of prostaglandin $F_{2\alpha}$ in relation to uterine contractions

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1 Introduction

Evidence for the participation of prostaglandins in the mechanism of labor has been accumulating over the last 10 years. Labor can be induced with intravenous administration of $PGF_{2\alpha}$ at term [1, 2, 13] and even before term [3]. During spontaneous as well as oxytocin-induced labor PGE and PGF concentrations in amniotic fluid rise [4, 14] and plasma levels of 13,14-dihydro-15-keto-PGF_2 (PGFM) also rise [11] although not until labor is in the active phase [6].

The failure to detect a singificant increase in circulating PGFM levels in early labor [6, 8] has cast some doubt on the importance of endogenous prostaglandin F generation for the initiation of labor. It is possible, however, that the uterine sensitivity to $PGF_{2\alpha}$ increases so much towards term that to elicit uterine contractions PGFM levels need not rise above normal levels. To investigate this possibility the present study was undertaken, the purpose of which was to correlate plasma concentrations of $PGF_{2\alpha}$ and PGFM to the increase in uterine activity when $PGF_{2\alpha}$ is infused i.v. at a low rate to pregnant women at term.

2 Materials and methods

The study was conducted on 16 women in whom induction of labor at term was indicated for reasons given in Table I. All gave consent to have up to 7 blood samples drawn in the course of the induction. Ten women were given $PGF_{2\alpha}$ infusions (Group B) and six controls were infused with physiological saline (Group A) for six hours before induction with $PGF_{2\alpha}$ was began.

The clinical characteristics of the patients of both groups are given in Table II. All had intact membranes and the groups were similar with the exception of parity. All in group B were multiparous whereas 4 of the 6 controls were primiparous.

The infusion of $PGF_{2\alpha}$ (Dinoprost®, 5 mg/l 0,9 % NaCl) was instituted at a rate of 1.5 µg/min and was increased stepwise to 3.0 µg/min at 30 min and to 6.0 µg/min at 90 min after infusion began.

Curriculum vitae

Born 1944 in Denmark, M.D. 1970, University of Copenhagen, Denmark. After various positions as intern and resident in Medicine, Surgery and Psychiatry, specialty training in Obstetrics and Gynecology. From 1978, Senior Registrar at the Aarhus Municipal Hospital and Lecturer in Obstetrics and Gynecology, University of Aarhus. 1981–82 Research Fellow in Obstetrics and Gynecology, Cornell University Medical College, New York City, working with ANNA-RIITTA FUCHS, *D. Sc. and* FRITZ FUCHS, *M. D., supported by a grant from* SANDOZ FOUNDATION, *New York.*

Tab. I. Indications for induction of labor

	Group A No.	Group B No.
Graviditas prolongata	1	5
Monosymptomatic proteinuria	2	1
Molimina gravidarum	1	1
Poliomyelitis antea	–	1
Rhesusimmunization	–	1
Diabetes, White Group A	1	1
Hypertensio arterialis	1	–
Total	6	10

The infusion was maintained at 6.0 µg/min until delivery; the infusion was discontinued after 6 hours if progressive labor was not established. The control group was infused with 0.9% NaCl for 6 hours. The cervical status was determined at examinations performed before and at 2, 4, and 6 hours after infusion began. Uterine activity and fetal well being were recorded with external electrocardiotocography. Artificial rupture of membranes was performed when BISHOP score was 9 or more.

Blood was drawn into heparinized, ice-cooled tubes before, and 0.5, 1, 2, 4, and 6 hours after infusion began, always before a vaginal examination. The blood samples were kept on ice and centrifuged immediately. The plasma was separated and acidified. The samples were then stored at – 20 °C until assayed for $PGF_{2\alpha}$ and PGFM with radioimmunoassays for $PGF_{2\alpha}$ and PGFM described earlier [6, 7]. The prostaglandins were extracted with ethylacetate-cyclohexane mixture (1 : 1) from plasma acidified to pH 4.5. The dried extracts were purified by silicic acid column chromotography (Biosil-A, BIORAD LABORATORIES, Richmond, California) before assay. Separation of bound and free ligand was done with dextran-charcoal. The antibody against $PGF_{2\alpha}$ (kindly donated by Dr. K. KIRTON, the UPJOHN Co. Kalamazoo, Michigan) cross-reacts almost 100% with $PGF_{1\alpha}$. The results are therefore expressed as PGF-like immuno-activity. The PGFM antibody was also a gift from Dr. K. KIRTON. It cross-reacts significantly (20%) with 15-keto-$PGF_{2\alpha}$ and has less than 1% cross-reactivity with PGE_2, PGA_2, and their 15-keto and 13,14-dihydro metabolites and to $PGF_{2\alpha}$. All solvents were from FISHER SCIENTIFIC (Fairlawn, New Jersey) and of spectranalyzed grade. Multitritiated $PGF_{2\alpha}$ and PGFM were used as labeled ligands. They were obtained from AMERSHAM (Arlington Heights, Illinois).

The detection limits (2 SD away from Bo) were 10 and 12 pg/tube for PGF and PGFM respectively. 50% displacement was obtained with 96.2 ± 14.2 and 133 ± 12 pg/tube for PGF and PGFM respectively. Intra-assay variations in the range of 50–200 pg were 6.8–8.2% and 3.4–6% for PGF and PGFM respectively and the inter-assay variations at the 50 pg levels were 18.4% and 8.6% respectively. Blank values due to solvents were deducted from the final calculations.

Statistical analysis was done by KRUSKAL-WALLIS nonparametric analysis of variance followed by DUNNETT's one tailed t-test, $p < 0.05$ was considered significant. Results are the mean SD for the clinical parameters and mean ± SE for the ± E plasma prostaglandin concentrations.

Tab. II. Clinical characteristics of the patient material. Data are means, range in parenthesis

	Group A n = 6	Group B n = 10
Age, years	29.5 (25–35)	29.9 (26–40)
Parity	1.5 (1–3)	2.7 (2–4)
Gestational age, weeks	39.5 (39–42)	40.9 (39–42)
Cervix, cm	1.33 (closed–3)	1.25 (closed–2)
BISHOP scores	4.8 (1–10)	4.2 (1–10)

3 Results

3.1 Uterine activity

Before the infusions began the patients had little or no uterine activity. In Group A, the mean frequency expressed as contractions per 10 min was 0.5 ± 0.5, and in Group B it was 0.1 ± 0.15. During infusion of $PGF_{2\alpha}$ all patients developed uterine contractions, with a mean interval to the onset of increased uterine contractions of

62.5 ± 62.1 min. The median value was 35 min, range 20 to 210 min. In 2 patients contractions appeared when the infusion rate was 1.5 µg/min, in 6 patients during infusion at the rate of 3.0 µg/min, and in two after the infusion rate was increased to 6.0 µg/min. The frequency of contractions then increased rapidly being 2.0 ± 2.1 at 1 hour, 2.8 ± 1.8 at 2 hours, and reaching a steady state of 3.5 ± 0.9 at 3 to 4 hours after infusion began (Fig. 1).

In the controls uterine activity remained unchanged in 5 and increased somewhat in one patient (from 1 per 30 min to 2 per 30 min) in the course of the 6 hours observation period.

3.2 Cervical changes

In Group B the BISHOP scores increased from a mean of 4.2 ± 1.8 before the infusion to 7.3 ± 3.1 at 6 or 8 hours after the $PGF_{2\alpha}$ infusion began. In Group A the change in BISHOP scores in the course of the 6 hours saline infusion was insignificant (from 4.8 ± 3.0 to 5.0 ± 2.9).

3.3 Outcome of induction: delivery

Five of the 10 patients in Group B delivered within 24 hours while only 1 in Group A delivered in less than 24 hours. The mean induction delivery interval in the 5 successful cases was 11.1 ± 7.4 hours. One patient in Group B had to be delivered by Caesarean section because of fetal distress that developed during the infusion of $PGF_{2\alpha}$. The four remaining patients required further induction and delivered 36 to 83 hours after the first infusion began.

In the control group two delivered spontaneously, 22 and 69 hours after saline infusion began, and 4 were induced with $PGF_{2\alpha}$ infusions, and they delivered within 5 days.

All infants had normal birth weights (mean: 3584 g, range 2900–4850 g) and APGAR scores with the exception of the infant delivered by Caesarean section who had APGAR score of 1 at 1 min, 6 at 5 min, and 10 at 10 min.

3.4 Plasma prostaglandin levels

The initial level of PGF was 47.0 ± 11.4 pg/ml in Group A and 37.7 ± 14.4 pg/ml in Group B. No significant rise was observed in the controls during the 6 hours infusion of saline (Fig. 1) whereas in Group B plasma PGF rose over initial levels in all patients. The rise became significant 2 hours after

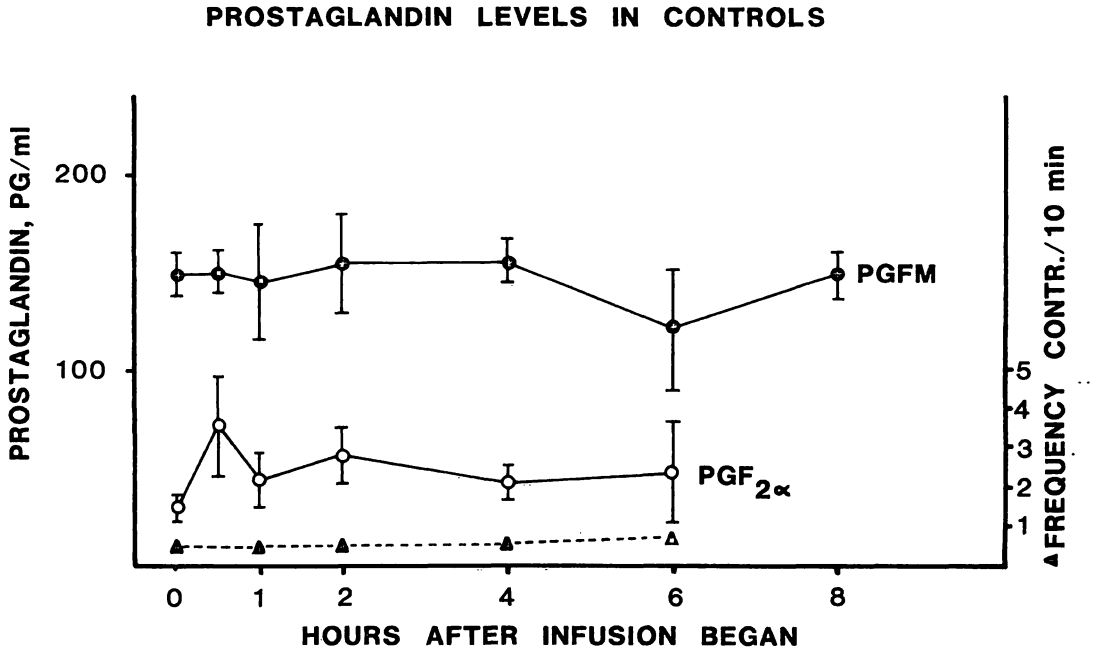

Fig. 1. Plasma prostaglandin levels before and during infusion of 0.9 % NaCl in 6 pregnant women at term (Group A). PGF: open circles; 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM): closed circles; frequency of uterine contractions is also shown: triangles. Values are mean ± SE.

infusion of $PGF_{2\alpha}$ began, when the rate was 6 μg/min. At the lowest rate, 1.5 μg/min, a rise was not detectable in any of the patients, with 3.0 μg/min the PGF levels increased in some but not all patients. Variations in plasma PGF levels were considerable even during the constant infusion of 6.0 μg/min. Incidentally the patient who had uterine hyperstimulation and in whom fetal bradycardia made Caesarean section necessary, had the highest PGF level of all, rising to almost 1000 pg/ml.

In Group A the concentration of PGFM did not change during the observation period, the levels hovered around 150 pg/ml (Fig. 1). In Group B, the concentration of PGFM rose very rapidly and was significantly increased 30 min after the infusion of $PGF_{2\alpha}$ began. The levels then increased in a dose dependent manner reaching a steady state of over 3 μg/ml at 2 hours (Fig. 2).

4 Discussion

The data presented in this study indicate that at rates required for uterine stimulation systemic administration of $PGF_{2\alpha}$ resulted in significant elevations of plasma PGFM levels, and at rates inducing labor-like uterine activity even the primary prostaglandin $F_{2\alpha}$ levels were raised. Both PGFM and PGF levels far exceeded the concentrations observed during spontaneous labor [6, 11] or oxytocin induced labor [12]. In contrast to the findings in spontaneous labor, plasma PGFM was significantly raised over late pregnancy levels already at or prior to the time when uterine contractile activity began to increase noticeably.

Oxytocin differs from $PGF_{2\alpha}$ in this respect. At term oxytocin is capable of inducing uterine contractions at infusion rates (1–2 mU/min) that do not raise circulating oxytocin levels singificantly

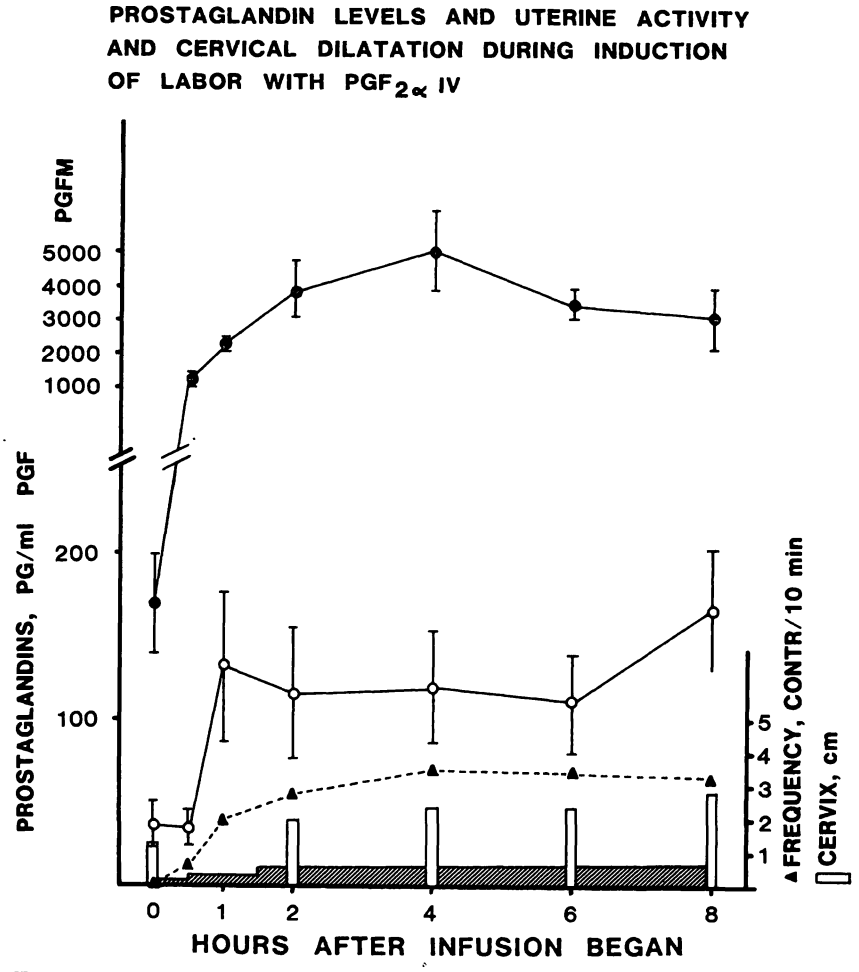

Fig. 2. Plasma prostaglandin levels before and during i.v. infusion of $PGF_{2\alpha}$ for induction of labor in 10 pregnant women at term (Group B), symbols as in Figure 1. Open bars represent cervical dilatation at the times indicated. Infusion rate was increased stepwise from 1.5 μg/min to 6 μg/min (stippled horizontal bar).

over values in late pregnancy plasma [6]. Thus the responsiveness of the human uterus to oxytocin increases proportionally more than that to $PGF_{2\alpha}$ in late pregnancy. A recent report by GIANNOPOULOS et al. [9] is in agreement with these observations. They found that the concentration of uterine PGE and F receptors changed very little during gestation; by contrast, we have found that oxytocin receptor concentrations increase about 100 fold from nonpregnant levels [5].

Thus, if prostaglandin $F_{2\alpha}$ production is causally related to the onset of spontaneous labor, the generation of this prostanoid must take place locally in the uterine tissues without reaching the systemic circulation in measurable quantities.

With regard to the clinical outcome of the $PGF_{2\alpha}$ infusions, the success rate of 50% was much lower than reported earlier using the same dosage [1]. The reason for this discrepancy may be the greater proportion of women with low BISHOP scores (< 4) in the present patient material than in the earlier report (30% vs 7%) although the correlation with success rate and BISHOP scores was not significant in the present study. Moreover, amniotomy was not performed until BISHOP score had reached 9, while in the earlier study [1] amniotomy was performed when cervix was 2 cm dilated regardless of the BISHOP score, and therefore all patients had amniotomy.

The cervical scores in the induction failures showed some improvement at the end of the 6 to 8 hours infusion, but the mean increment, 1.25 points over 8 hours was not very impressive in spite of strong uterine activity even in these patients. Induction of labor by means of iv $PGF_{2\alpha}$ infusions in high-risk pregnancies does therefore not seem to be better than induction by means of endocervical PGE_2 gel application [7, 10, 15]. The success rate in induction by means of iv infusions of $PGF_{2\alpha}$ does therefore not justify the inconvenience and unpleasant side-effects associated with the method, in comparison to the minimal side-effects associated with local application of PGE_2 followed by low dose of oxytocin if necessary.

Summary

The concentrations of plasma $PGF_{2\alpha}$ and its main metabolite, 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) were measured in serial samples of blood collected in 10 pregnant women at term who were given iv infusions of low doses of $PGF_{2\alpha}$ for induction of labor. Six other women served as controls and were given saline infusions. Uterine contractions began with a mean latency of 62 min in the $PGF_{2\alpha}$ infused women, in controls uterine activity remained unchanged. Plasma PGFM levels had increased significantly 30 min after $PGF_{2\alpha}$ infusion began, rising thereafter in a dose dependent manner. Plasma $PGF_{2\alpha}$ also rose reaching a steady state at 2 hours. No significant changes were observed in the controls. The 6-h infusion resulted in delivery in 5 of the 10 women, in the 5 others the cervical scores increased only by 1.25 points on the average and further treatment was needed to achieve delivery, although prostanoid levels rose to similar levels in all. The data show that when uterine contractions are induced by systemic $PGF_{2\alpha}$, the levels of PGFM are significantly raised. In spontaneous labor uterine contractions begin long before plasma PGFM rises. Thus, if endogenous $PGF_{2\alpha}$ generation is involved in the initiation of uterine contractions during spontaneous labor, it must be synthetized in the myometrium at quantities too low to raise the levels of circulating PGFM.

Keywords: Induction of labor, plasma prostaglandin $F_{2\alpha}$, plasma 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$, prostaglandin $F_{2\alpha}$, uterine contractions.

Zusammenfassung

Höhe der PG-$F_{2\alpha}$- und 13,14-dihydro-15-keto-PG-$F_{2\alpha}$-Plasmaspiegel bei Geburtseinleitungen mit PG-$F_{2\alpha}$-Infusionen in Relation zur Wehentätigkeit

Wir bestimmten die Plasmakonzentrationen von $PGF_{2\alpha}$ und 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) als Hauptmetabolit in mehreren Blutproben von 10 Frauen am Termin. Sie erhielten zur Geburtseinleitung Infusionen mit $PGF_{2\alpha}$ in niedriger Dosierung. Die Kontrollgruppe bestand aus 6 Frauen, bei denen NaCl infundiert wurde. Die Wehentätigkeit setzte bei $PGF_{2\alpha}$-Infusion nach einer mittleren Latenzzeit von 62 Minuten ein. In der Kontrollgruppe waren keine Veränderungen zu beobachten. Der PGFM-Spiegel zeigte 30 Minuten nach Beginn der $PGF_{2\alpha}$-Infusion einen signifikanten Anstieg, danach war der Anstieg dosisabhängig. Auch die $PGF_{2\alpha}$-Spiegel stiegen an und erreichten nach 2 Stunden einen Steady-state. In der Kontrollgruppe kam es wiederum nicht zu Veränderungen. Eine Infusion über 6 Stunden führte bei 5 der 10 Frauen zur Entbindung. Bei den anderen 5 Frauen änderte sich der Zervix-Score um durchschnittlich 1,25

Punkte, so daß eine weitere Behandlung notwendig war. Der Anstieg der PG-Spiegel war jedoch ähnlich wie bei den übrigen Verläufen. Unsere Ergebnisse zeigen, daß bei einer Wehentätigkeit, die durch systemische $PGF_{2\alpha}$-Gabe induziert wurde, die PGFM-Spiegel signifikant ansteigen. Bei Spontangeburten beginnt die Wehentätigkeit lange vor dem Anstieg der PGFM-Plasmaspiegel. Wenn eine endogene $PGF_{2\alpha}$-Bildung bei der Induktion der Wehentätigkeit bei Spontangeburten beteiligt ist, muß $PGF_{2\alpha}$ im Myometrium synthetisiert werden, und zwar in Mengen, die zu klein sind, um die Spiegel des zirkulierenden PGFM anzuheben.

Schlüsselwörter: Geburtseinleitung, Prostaglandin $F_{2\alpha}$ im Plasma, 13,14-dihydro-15-ketoprostaglandin $F_{2\alpha}$ im Plasma, Prostaglandin $F_{2\alpha}$, Wehentätigkeit.

Résumé

Taux plasmatiques de prostaglandines $F_{2\alpha}$ et de 13,14-dihydro-15-ceto-prostaglandines $F_{2\alpha}$ chez les femmes en cours d'induction de travail par perfusion i.v. de prostaglandines $F_{2\alpha}$ relations avec les contractions utérines

On a mesuré les concentrations plasmatiques de $PGF_{2\alpha}$ et de son métabolite principal, la 13,14-dihydro-ceto-$PGF_{2\alpha}$ (PGFM) dans des échantillons sanguins prélevés en série chez 10 femmes enceintes à terme dont le travail était déclenché par des perfusions de faibles doses de $PGF_{2\alpha}$. Six autres femmes on servi de contrôles et on reçu des perfusions de serum salé.

Les contractions utérines ont débuté au bout d'un temps de latence moyen de 62 minutes chez les femmes recevant les $PGF_{2\alpha}$, tandis que chez les témoins, l'activité utérine est demeurée inchangée.

Le taux plasmatique de PGFM s'est élevé de façon significative 30 minutes après le début de la perfusion de $PGF_{2\alpha}$, avec une élévation ultérieure dose dépendante.

Les $PGF_{2\alpha}$ se sont aussi élevées pour atteindre un plateau stable au bout de 2 heures.

Les 6 heures de perfusion ont permis l'accouchement chez 5 femmes sur 10, chez les 5 autres les scores cervicaux ne se sont améliorés en moyenne que de 1,25 points et un traitement supplémentaire a été nécessaire pour obtenir l'accouchement bien que les taux de prostanoides se soient élevés de façon similaire chez toutes les femmes.

Les données montrent que quand les contractions utérines sont induites par des $PGF_{2\alpha}$ systémiques les taux de PGFM s'élèvent de façon significative.

Lors du travail spontané, les contractions utérines commencent longtemps après l'élévation plasmatique de PGFM.

De telle sorte que, si l'on implique la synthèse de $PGF_{2\alpha}$ endogènes dans l'initiation des contractions utérines relatifs aux accouchements spontanés, ces prostaglandines endogènes doivent être synthétisées dans le myomètre en quantité assez faible pour ne pas élever les taux de PGFM circulantes.

Mots-clés: Contractions utérines, déclenchement du travail, prostaglandines $F_{2\alpha}$, prostaglandines $F_{2\alpha}$ plasmatiques, prostaglandines 13,14-dihydro-15-céto-prostaglandines $F_{2\alpha}$ plasmatiques.

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